BEMA Fentanyl). The preliminary data also indicates that Fentanyl SL stays close to T_{max} for 100 minutes translating to pain relief for a longer time.

Example 21

Pharmacokinetic Profile of Fentanyl Sublingual (SL) Spray

In Example 21, a five-treatment, five-sequence, five-period crossover study of fentanyl SL spray was conducted under fasted conditions in up to 70 healthy subjects. The objectives were to determine the pharmacokinetics of five difference doses (Part A), and to assess the impact of temperature and pH in the oral cavity on the relative bioavailability at a fixed dose (Part B). Healthy subjects had to meet pre-specified eligibility criteria. Plasma samples were obtained at time points of 0, 5, 10, 20, 30, 40 min, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 16, 24 and 36 h post-dose and analyzed for fentanyl using a validated LC-MS-MS procedure.

53 subjects were enrolled in part A. Administration of fentanyl SL spray was dose-proportional over the 100 mcg to 800 mcg dose ranges. Fentanyl concentrations increase rapidly following administration, being above the LLOQ within 5 minutes, reaching 60.6% of the peak plateau by 10 minutes and 86.6% of the peak plateau by 20 minutes post dose. Fentanyl concentrations showed a relatively long plateau about the peak value (>80% of Cmax) that lasted approximately 2 hours.

14 subjects were enrolled in part B. Varying the pH and temp of the oral cavity did not affect the PK profile. No SAEs were noted. AEs were observed in 31 subjects in part A. 46 were probably related to study treatment, and 29 were possibly related. During part B, AEs were observed in 9 subjects. 7 were probably related to study treatment, and 17 were possibly related. AEs were emesis or nausea.

The results of this study support the rationale for assessing efficacy in patients with breakthrough pain. The dose proportionality supports a rationale for predictable dosing favorable for titration.

Example 22

Comparative Bioavailability of Fentanyl Sublingual (SL) Spray, IV Fentanyl Citrate and Actiq

In Example 22, a single-dose, open-label, randomized, three-period, three-treatment crossover study with a washout period of at least seven days between study periods was conducted at a phase I contract clinic under good clinical practice guidelines. 40 healthy volunteers were enrolled, having met pre-specified eligibility criteria. Subjects received a single dose of fentanyl SL spray 400 mcg, Actiq 400 mcg lozenge, and fentanyl citrate 100 mcg by IV injection over 5 minutes in 3 separate treatment periods. Plasma samples were obtained at time points of 0, 5, 10, 20, 30, 40 min, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 16, 24 and 36 h post-dose and analyzed for fentanyl using a validated LC-MS-MS procedure.

The results showed that compared to intravenous administration, the median value for absolute bioavailability of fentanyl SL spray was 60.8%; bioavailability of Actiq was 46.6%. The median value for relative bioavailability of Fentanyl SL Spray to that of Actiq was 135%. Systemic absorption of fentanyl SL was more rapid than Actiq. Subjects were monitored for any adverse events. AEs were reported in 15 of the 40 subjects. All of the AEs were mild. Two of the AEs were probably related to the study drug (both were sublingual burning at 400 mcg). Three of the AEs were possibly related to the study treatment (headache, dizziness, and dry throat all reported at 400 mcg).

The results of this study support the rationale for assessing efficacy in patients with breakthrough pain.

Many other variations of the present invention will be apparent to those skilled in the art and are meant to be within the scope of the claims appended hereto, including but not limited to the particular unit dose or bi-dose devices and the particle size range of fentanyl produced, as well as other numerical parameters described in the examples, and any combination thereof.

The invention claimed is:

1. A sublingual spray formulation for the treatment of pain comprising:

from about 0.1% to about 0.8% by weight of fentanyl, a free base or a pharmaceutically acceptable salt thereof;

(ii) from about 50% to about 60% by weight of ethanol; and

(iii) from about 4% to about 6% by weight of propylene glycol,

wherein the formulation provides a mean T_{max} of about 1.28+/−0.60, is propellant-free and comprises droplets having a mean diameter of at least about 10 microns.

2. The formulation of claim **1**, wherein the concentration of fentanyl, a free base or a pharmaceutically acceptable salt thereof, or a derivative thereof is from about 1 mg/mL to about 8 mg/mL.

3. The formulation of claim **1**, wherein the concentration of fentanyl, a free base or a pharmaceutically acceptable salt thereof, or a derivative thereof is selected from the group consisting of about 1 mg/mL, about 2 mg/mL, about 4 mg/mL, about 6 mg/mL and about 8 mg/mL.

4. The formulation of claim **1**, which provides a mean C_{max} of about 0.813 ng/ml+/−0.252 based on a sublingual dose of about 400 mcg fentanyl when administered to humans.

5. The formulation of claim **1**, which provides a dosage amount of fentanyl, a free base or a pharmaceutically acceptable salt thereof, or a derivative thereof selected from the group consisting of about 100 mcg, about 200 mcg, about 600 mcg and about 800 mcg, and provides a mean C_{max} which is substantially dose proportional to the formulation containing a 400 mcg fentanyl dosage amount, when administered to humans.

6. The formulation of claim **1**, which provides a substantially dose proportional mean C_{max} based on a mean C_{max} of about 0.813 ng/ml+/−0.252 for a 400 mcg fentanyl dose when administered to humans.

7. The formulation of claim **1**, which, when administered to humans, provides a mean T_{max} selected from the group consisting of: about 1.12 hours when the formulation provides a 100 mcg dose, about 1.04 hours when the formulation provides a 200 mcg dose, about 0.97 hours when the formulation provides a 400 mcg dose, about 0.987 hours when the formulation provides a 600 mcg dose, and about 1.06 hours when the formulation provides a 800 mcg dose.

8. The formulation of claim **1**, which, after administration to humans, provides a plasma concentration selected from the group consisting of: about 60% of the mean C_{max} in about 10 minutes, about 86% of the mean C_{max} by about 20 minutes and a combination thereof.

9. The formulation of claim **1**, which provides for about 2 hours, a plasma concentration after administration to humans that is greater than about 80% of the mean C_{max}.